JACC Vol. 21, No. 2
February 1993:356–8

Editorial Comment

Myocardial Contrast Echocardiography Has the Potential for the Assessment of Coronary Microvascular Reserve*

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What is coronary microvascular reserve? In the presence of a coronary vasodilator, both coronary blood flow and myocardial intravascular volume increase. The latter increase occurs as a result of dilation of coronary microvessels as well as recruitment of previously collapsed capillaries, resulting in an increase in coronary blood flow (1). Traditionally, the effect of a coronary vasodilator has been assessed by measuring changes in blood flow alone (2–4); changes in myocardial blood volume have not been measured. Because the changes in coronary flow occur as a *result of* changes in myocardial blood volume, conditions that will preclude an appropriate increase in coronary flow in the presence of coronary vasodilators will do so by not allowing myocardial blood volume to increase by the expected amount.

Under normal conditions, after intravenous infusion of adenosine, flow through a myocardial bed can increase by a factor of 5, whereas myocardial volume increases 2-fold, with the flow/volume ratio increasing 2.5-fold (5). If half of the myocardial microvasculature is functionally abnormal, coronary flow may increase by only a factor of 2.5 instead of 5 and myocardial volume by only a factor of 1.5 instead of 2. The flow/volume ratio will therefore increase by only a factor of 1.6 instead of 2.5. Similarly, if only one fourth of the microvasculature is functionally normal, coronary flow may increase by only a factor of 1.25 instead of 5 and myocardial blood volume by only a factor of 1.25 instead of 2, with the flow/volume ratio remaining unchanged instead of increasing by 2.5. Measuring the flow/volume ratio will therefore provide clinical information on coronary microvascular reserve similar to that provided by measuring flow alone.

In the study of Porter and colleagues (6) reported in this issue of the Journal, these investigators injected sonicated albumin microbubbles into the left main coronary artery before and after intracoronary injection of papaverine into patients with no epicardial coronary disease. They found that changes in myocardial transit rates of these microbubbles correlated well with changes in coronary flow velocity measured with an intracoronary Doppler flow catheter. Because the transit rate of a tracer equals the flow/volume ratio, as discussed, any agent that will increase both myocardial blood volume and flow (and all coronary vasodilators will do so) will increase transit rate less than flow, which is exactly what Porter and colleagues found.

The all important input function! Other than changes in flow and volume, the myocardial transit rate of microbubbles is influenced by the input function (shape of the time-concentration curve of the bubbles that the myocardium "sees"), which in turn is affected by the method and the site of injection. Assuming that the bubbles are injected every time in the same manner, then the site of injection becomes an important determinant of the input function. If bubbles are injected into the left anterior descending coronary artery (Fig. 1A) as a delta function (Fig. 1B), the output function from the myocardium will resemble a gamma-variate form (Fig. 1C) (7,8). Providing the method of injection remains constant, the transit rate of the bubbles through the myocardium will equal the flow/volume ratio and the ratio of the transit rate after and before a coronary vasodilator will indicate coronary microvascular reserve.

The farther the injection site from the sampling site (the myocardium in this case), the more likely it is that the input function may no longer be a delta function and will become more spread out to resemble a gaussian function (Fig. 1D). The width of the gaussian will depend on the time it takes for the bubbles to travel from the site of injection to the myocardium, which in turn depends on the flow through the vessel. In such an instance, the lagged-normal density function (Fig. 1E) (9) may provide a more appropriate fit to the myocardial time-intensity plot than the gamma-variate function. When the bubbles are injected directly into the left anterior descending artery, because it is the same flow through the artery that will influence *both* the input and output functions, the transit rate derived from the output function will correlate with flow through the vessel even if the input function deviates slightly from a delta function (8).

Porter and colleagues (6) injected bubbles into the left main coronary artery and derived time-intensity plots from the left anterior descending artery bed. In this case, the flow through the left main coronary artery will influence the width of the input function, independent of the flow in the left anterior descending artery. Because the patients studied by Porter et al. (6) had normal coronary vessels, the magnitude of increase in flows through both the left anterior descending

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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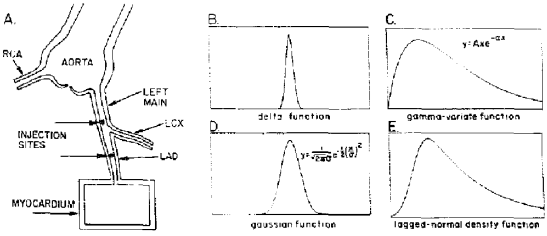

Figure 1. Diagrams depicting the effect of site and method of injection on input function. **A,** Regions within the left coronary system proximal to the left anterior descending (LAD) artery bed where the microbubbles can be injected. The farther one gets from the myocardial bed, the more likely it is that the input function will not resemble a delta function. **B,** Delta function input. **C,** Output function resembling a gamma-variate form, where α is transit rate of the bubbles in a two-compartment model and equals the ratio of the flow/volume distribution. **D,** Example of input function assuming a gaussian distribution, where σ represents the width of the gaussian. The output function resembles a lagged-normal density function (**E**) that is obtained by solving the differential equation $dy/dx = \alpha[G(x) - y]$, where α = flow/volume. LCX = left circumflex coronary artery; RCA = right coronary artery.

bed and the left main artery was the same; therefore, changes induced in both the input and the output function widths were in the *same* direction. Consequently, Porter and colleagues were able to demonstrate a relation between left anterior descending artery flow and microbubble transit rates through that bed even though bubbles were injected into the left main artery.

Consider now a situation where the left anterior descending artery has a severe stenosis precluding any increase in flow through it after administration of papaverine, while the flow through the left circumflex artery increases fivefold. If baseline flow through the two arteries was the same, then flow through the left main artery will increase threefold and will affect the width of the input function in a manner that is *dissimilar* to the way in which flow through the left anterior descending artery will affect the output function (8). For the same flow in the left anterior descending artery, therefore, the output function will be different before and after papaverine. The two output functions from the same bed cannot be compared unless the input functions are known. Comparisons of output functions between different beds may, however, provide relative changes in microvascular reserve (10).

Because Porter et al. (6) injected the bubbles slowly over 6 s rather than as a delta function, the input function was probably spread out more as a result of the method rather than the site of injection. This method of injection resulted in a gaussian distribution of the output function as can be appreciated from Figure 2 in their study. A lagged-normal density function would have provided a better fit to their data than a gamma-variate function (9). Although more computer-intensive (11), the lagged-normal density function has the advantage that as long it has a gaussian distribution, the input function need not be constant and can be mathematically adjusted from the output function (9,11,12).

Limitations of the current study. The results of the study by Porter and colleagues (6) show that coronary microvascular reserve can be assessed in patients with myocardial contrast echocardiography. The likelihood that the considerable noise in their data is related to methodologic issues is confirmed by their large interobserver and intraobserver errors, which are far greater than the biologic variability in regional myocardial flow (13).

These investigators used an on-line system that is still under development. The version they used provides a very small region of interest. Because there is significant spatial heterogeneity in flow within the same myocardial bed (13), sampling just a small portion of the bed can result in significant noise. Additionally, enlarging the region of interest by nine times would alone have improved the signal to noise ratio by three times and improved their observer variability (14).

Analysis of data on-line in real time with a fixed region of interest over myocardium that moves with respiration precluded sampling of video intensity within the same region in each frame, also resulting in significant variability in the measured video intensity. Capturing data in cine loop and then moving the region of interest manually to the same area of the myocardium in each end-diastolic frame may be a better option. Obviously, an automatic method of image alignment using cross correlation or other techniques would be even more accurate and definitely less tedious (14).

Finally, as stated, because of the slow rate of injection of contrast medium, application of a lagged-normal density rather than a gamma-variate function to the myocardial time-intensity plots would have resulted in a better fit and less noise. Future developments in commercial analysis packages will need the incorporation of different curve-fitting algorithms for different types of time-intensity plots, and users will have to become familiar with them. For

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instance, in the operating room, because the microbubbles adhere to the microvessels in the hypoxic cardioplegia-arrested heart, the time-intensity plots resemble neither a gamma-variate nor a gaussian form. Instead, a general exponential function provides the best fit (15).

Summary. Coronary vasodilators increase coronary flow by increasing myocardial blood volume. Diseases affecting the coronary microvasculature will affect vasodilator-induced changes in coronary flow by inhibiting changes in myocardial blood volume. In such cases, when myocardial time-intensity curves after administration of a vasodilator are compared with those at baseline, a less than anticipated increase in microbubble transit rates will be noted. As long as we understand what we are measuring in the context of where and how we inject the bubbles, we can begin to define the role of myocardial contrast echocardiography in assessing changes in coronary microvascular reserve. It is also conceivable that because myocardial contrast echocardiography can assess changes in myocardial flow/volume relations rather than just changes in flow, this technique could be used to provide additional insights into the mechanisms of action of different coronary vasodilators and into the pathophysiology of various diseases affecting the coronary microvasculature. Finally, with the advent of commercially available microbubbles, robust on- and off-line analysis algorithms and intracardiac imaging, myocardial contrast echocardiography may become an invaluable adjunct to coronary angiography for determining the pathophysiologic significance of coronary disease in individual patients.

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